

WHAT IS CLAIMED IS:

1. A method of assessing the effect of a test condition on G-protein-coupled receptor (GPCR) pathway activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an interacting protein partner as a fusion to another mutant form of enzyme;

b) exposing the cell to a ligand for said GPCR under said test condition; and

c) monitoring activation of said GPCR by complementation of said reporter enzyme;

wherein increased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates increased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition, and decreased reporter enzyme activity in the cell compared to that which occurs in the absence of said test condition indicates decreased GPCR interaction with its interacting protein partner compared to that which occurs in the absence of said test condition.

2. A method according to Claim 1, wherein the test condition is the presence in the cell of a kinase.

3. A method according to Claim 1, wherein the test condition is the presence in the cell of a G-protein.

4. A method according to Claim 1, wherein the test condition is the exposure of the cell to a compound selected from GPCR agonists and GPCR antagonists.

5. A method according to Claim 1, wherein the test condition is co-expression in the cell of a second receptor.

6. A method according to Claim 5, wherein the second receptor is a GPCR receptor.

7. A method according to Claim 5, wherein homo-dimerization of GPCR is determined.

8. A method according to Claim 5, wherein hetero-dimerization of GPCR is determined.

9. A method for screening a β -arrestin protein or an unidentified arrestin or arrestin-like protein or fragment and mutant form thereof for the ability to bind to activated GPCRs, comprising:

a) providing a cell that:

i) expresses at least one GPCR as a fusion protein to a reporter enzyme; and

ii) contains a conjugate comprising a test β -arrestin protein as a fusion protein

with another reporter enzyme;

b) exposing the cell to a ligand for said at least one GPCR; and

c) detecting enzymatic activity of the complemented reporter enzyme;

wherein an increase in enzymatic activity in the cell indicates β -arrestin protein

binding to the activated GPCR.

10. A method for screening a test compound for G-protein-coupled receptor (GPCR) agonist activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme;

b) exposing the cell to a test compound; and

c) detecting complementation of said reporter enzyme;

wherein increased reporter enzyme activity after exposure of the cell to the test compound indicates GPCR agonist activity of the test compound.

11. A method according to Claim 10, wherein the cell expresses a GPCR whose function is known.

12. A method according to Claim 10, wherein the cell expresses a GPCR whose function is unknown.

5 13. A method according to Claim 10, wherein the cell expresses an odorant or taste GPCR.

14. A method according to Claim 10, wherein the cell expresses a GPCR a β -adrenergic GPCR.

15. A method according to Claim 10, wherein the cell is selected from the group consisting of mammalian cells, cells of invertebrate origin, plant cells and protozoa cells.

16. A method according to Claim 10, wherein the cell endogenously expresses a GPCR.

17. A method according to Claim 10, wherein the cell has been transformed to express a GPCR not endogenously expressed by such a cell.

15 18. A method of screening a test compound for G-protein-coupled receptor (GPCR) antagonist activity, comprising:

a) providing a cell that expresses a GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin protein as a fusion to another mutant form of enzyme;

b) exposing the cell to said test compound;

20 c) exposing the cell to an agonist for said GPCR; and

d) detecting complementation of said reporter enzyme;

where exposure to the agonist occurs at the same time as, or subsequent to, exposure to the test compound, and wherein decreased reporter enzyme activity after exposure of the

cell to the test compound indicates that the test compound is an antagonist for said GPCR.

19. A method of screening a cell for the presence of a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist, comprising:

a) providing a cell, said cell containing a conjugate comprising a β -arrestin protein as a fusion protein with a reporter enzyme;

b) exposing the cell to a GPCR agonist; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase in enzymatic activity after exposure of the cell to the GPCR agonist indicates that the cell contains a GPCR responsive to said agonist.

20. A method of screening a plurality of cells for those cells which contain a G-protein-coupled receptor (GPCR) responsive to a GPCR agonist, comprising:

a) providing a plurality of cells, said cells containing a conjugate comprising a β -arrestin protein as a fusion protein with a reporter enzyme;

b) exposing the cells to a GPCR agonist; and

c) detecting enzymatic activity of the reporter enzyme;

wherein an increase in enzymatic activity after exposure to the GPCR agonist indicates β -arrestin protein binding to a GPCR, thereby indicating that the cell contains a GPCR responsive to said GPCR agonist.

21. A method according to Claim 20, wherein the plurality of cells are contained in a tissue.

22. A method according to Claim 20, wherein the plurality of cells are contained in an organ.

23. A method according to Claim 20, wherein step (b) comprises exposing the cells to a plurality of GPCR agonists or ligand libraries.

24. A substrate having deposited thereon a plurality of cells, said cells expressing at least one GPCR as a fusion protein to one mutant form of reporter enzyme and an arrestin
5 protein as a fusion to another mutant form of enzyme.

25. A substrate according to Claim 24, wherein the substrate contains an enzyme-labile chemical group which, upon cleavage by the reporter enzyme, releases a product measurable by colorimetry, fluorescence or chemiluminescence.

26. A substrate according to Claim 24, wherein the substrate is made of a material selected from glass, plastic, ceramic, semiconductor, silica, fiber optic, diamond, biocompatible monomer and biocompatible polymer materials.

27. A method of detecting G-protein-coupled receptor (GPCR) pathway activity in a cell expressing at least one GPCR and containing β -arrestin protein as a fusion protein with a reporter enzyme; wherein said enzymatic activity indicates activation of the GPCR pathway.

28. A method according to Claim 27, where the cells are deposited on a substrate prior to detecting said enzymatic activity.

29. A method according to Claim 27, wherein said cell is contained in a tissue.

30. A method according to Claim 27, wherein said cell is contained in an organ.